# LEMD3 gene

LEM domain containing 3

## Normal Function

The *LEMD3* gene provides instructions for making a protein that is located in the inner membrane of the nuclear envelope. The nuclear envelope is a cell structure that surrounds the nucleus, acting as a barrier between the nucleus and the rest of the cell.

The LEMD3 protein helps control two chemical signaling pathways called the transforming growth factor beta (TGF-β) pathway and the bone morphogenic protein (BMP) pathway. Signaling through these pathways turns on (activates) proteins called Smads, which attach (bind) to specific areas of DNA to activate certain genes. The TGF-β and BMP pathways regulate various cellular processes, including cell growth and division (proliferation), the process by which cells mature to carry out special functions (differentiation), and the self-destruction of cells (apoptosis). These pathways are also involved in the growth of new bone.

The LEMD3 protein interacts with Smads to reduce signaling through the BMP and TGF-β pathways. In this way, the LEMD3 protein helps keep signaling at normal levels within the cell.

## Health Conditions Related to Genetic Changes

Buschke-Ollendorff syndrome

At least 23 mutations in the *LEMD3* gene have been found to cause Buschke-Ollendorff syndrome, a rare connective tissue disorder. (Connective tissues provide strength and flexibility to structures throughout the body.) The condition is characterized by connective tissue nevi and osteopoikilosis. Connective tissue nevi are small, noncancerous lumps on the skin that are widespread in people with this disorder. Osteopoikilosis is a skeletal abnormality characterized by small, round areas of increased bone density that can be seen on x-rays.

Each of the known *LEMD3* gene mutations prevents the production of functional LEMD3 protein from one copy of the gene in each cell, which reduces the total amount of LEMD3 protein by about half. A shortage of this protein prevents it from controlling BMP and TGF-β signaling effectively, leading to increased signaling through both of these pathways. Studies suggest that the enhanced signaling increases the formation of bone tissue, resulting in areas of overly dense bone. It

is unclear how the abnormal signaling is related to the development of connective tissue nevi in people with Buschke-Ollendorff syndrome.

other disorders

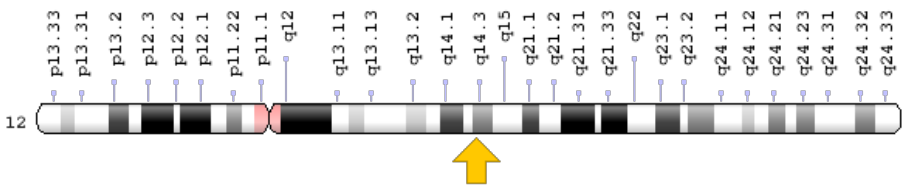
*LEMD3* gene mutations have also been found in people with isolated osteopoikilosis, a condition involving areas of increased bone density that occur without the connective tissue nevi that characterize Buschke-Ollendorff syndrome. Occasionally, osteopoikilosis occurs with another, more severe skeletal abnormality called melorheostosis. This abnormality causes the outer layers of bones to become overly thick and dense, and it tends to be limited to one arm or leg. Melorheostosis can be associated with pain, stiffness, and restricted joint movement that worsen over time.

Researchers are working to determine how *LEMD3* gene mutations cause Buschke-Ollendorff syndrome in some people and isolated osteopoikilosis or osteopoikilosis with melorheostosis in others. In some cases, the same mutation has been found to cause all of these conditions in different members of a single family. Each of the known mutations reduces the amount of functional LEMD3 protein that is produced in cells, which abnormally enhances BMP and TGF-β signaling and leads to areas of increased bone density.

## Chromosomal Location

Cytogenetic Location: 12q14.3, which is the long (q) arm of chromosome 12 at position 14.3

Molecular Location: base pairs 65,169,571 to 65,248,361 on chromosome 12 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)




Credit: Genome Decoration Page/NCBI

## Other Names for This Gene

- inner nuclear membrane protein Man1
- integral inner nuclear membrane protein
- LEM domain-containing protein 3

- MAN1
- MAN1_HUMAN

## Additional Information & Resources

Educational Resources

- Developmental Biology (sixth edition, 2000): The Smad Pathway Activated by TGF-β Superfamily Ligands
  https://www.ncbi.nlm.nih.gov/books/NBK10043/figure/A1057/
- Molecular Biology of the Cell (fourth edition, 2002): Signal Proteins of the TGF-β Superfamily Act Through Receptor Serine/Threonine Kinases and Smads
  https://www.ncbi.nlm.nih.gov/books/NBK26822/#A2874
- The Cell: A Molecular Approach (second edition, 2000): The Nuclear Envelope and Traffic between the Nucleus and Cytoplasm
  https://www.ncbi.nlm.nih.gov/books/NBK9927/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28LEMD3%5BTIAB%5D%29+OR+%28MAN1%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

OMIM

- LEM DOMAIN-CONTAINING PROTEIN 3
  http://omim.org/entry/607844

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_LEMD3.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=LEMD3%5Bgene%5D
- HGNC Gene Family: LEM domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/1087
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=28887

- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/23592
- UniProt
  http://www.uniprot.org/uniprot/Q9Y2U8

## Sources for This Summary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